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NEONATAL VACCINATION OF LOW BIRTH WEIGHT INFANTS IN GHANA

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ABSTRACT

Objectives:

Global vaccination policy advocates for identifying and targeting groups who are under-served by vaccination to increase equity and uptake. We investigated whether birth weight and other factors are determinants of neonatal BCG vaccination, in order to identify infants under-served by vaccination.

Methods:

We used logistic regression to calculate adjusted odds ratios (AOR) for the association between birth weight (categorised as non-low birth weight (NLBW) (≥2.50kg) and low birth weight (LBW) (2-2.49kg, 1.50-1.99kg and <1.50kg) and non-vaccination with BCG at the end of the neonatal period (0-27 days). We assessed whether this association varied by place of delivery and infant illness. We calculated how BCG timing and uptake would improve by ensuring the vaccination of all facility-born infants prior to discharge.

Results:

There was a strong dose response relationship between LBW and not receiving BCG in the neonatal period (p-trend<0.0001). Infants weighing 1.50-1.99kg had odds of non-vaccination 1.6 times (AOR=1.64; 95%CI:1.30-2.08), and those weighing <1.50kg 2.4 times (AOR=2.42; 95%CI:1.50-3.88) those of NLBW infants. Other determinants included place of delivery, distance to the health facility and socioeconomic status. Neither place of delivery nor infant illness modified the association between birth weight and vaccination (p-interaction all >0.19). Facility-born infants were vaccinated at a mean of 6 days, suggesting they were not vaccinated in the facility at birth but were referred for vaccination.

Conclusions

LBW is a risk factor for neonatal vaccination, even for facility-born infants. Ensuring vaccination at facility births would substantively improve timing and equitable BCG vaccination.

INTRODUCTION

Approximately 3 in 10 deaths among children aged 1-59 months are vaccine preventable,[1] and one in five infants is not fully vaccinated by age 52 weeks. Substantive socio-demographic inequities in vaccination remain.[2] Many infants are vaccinated late.[3] [4] The latest global vaccination policy highlights the need to identify and target those under-served by vaccination, in order to increase equity and uptake.[2]

Using data from a large prospective population-based trial of neonatal vitamin A supplementation in Kintampo in rural Ghana (Neovita), we previously reported that LBW infants are more likely to be delayed in their DTP1 and DTP3 vaccination.[5] For postneonatal vaccines, the onus is on the care-taker to bring the infant for vaccination at scheduled times. Any vaccination delay may be partly due to care-taker hesitancy to bring infants for vaccination, possibly due to their fragility or illness.[6] This may not be the case for neonatal vaccinations, as the large proportion of facility-born infants automatically have opportunities for vaccination. Consequently, vaccine determinants may differ in these periods. In an effort to identify further those under-served by vaccination, we investigated birth weight and other factors as determinants of neonatal vaccination.

In countries with a high prevalence of tuberculosis, the World Health Organisation (WHO) recommends "BCG be given to all healthy neonates, or as soon as possible after birth".[7] In addition to BCG, in Ghana, a birth dose of polio (OPVB) is recommended at a maximum age of two weeks,[8] as part of a four dose schedule. Hepatitis B is not recommended in the schedule. The WHO recommends BCG vaccination by intradermal injection to the arm,[7] whereas OPVB is given orally.[9] We selected BCG as an indicator for neonatal vaccination due to its longer recommended window for administration (throughout the neonatal period), and on the basis that any hesitancy relating to the vaccination of fragile infants would be more evident for injected vaccines.

Low birth weight is not a contraindication to BCG vaccination. [7] The WHO advises that infants should receive all due vaccines prior to discharge from health facilities.[10] Therefore, infants born in health facilities should be vaccinated prior to discharge home.

Infant illness has been cited as a reason for non-vaccination by both caregivers and vaccine-providers.[6] Given this, and the opportunities for vaccination associated with being born in a facility, as secondary objectives we investigated whether the association between birth weight and neonatal BCG vaccination varied by place of delivery and infant illness.

MATERIALS AND METHODS

Neovita was undertaken at the Kintampo Health Research Centre (KHRC) in rural Ghana. Trial methods have been described in detail elsewhere.[11,12]

In Ghana, neonatal vaccines are given either at the health facility following delivery, or at child health clinics in health facilities or Community Health Planning System (CHPS) compounds in the community. Monthly mobile outreach clinics target areas lacking health facilities or CHPS compounds. Following vaccination, the vaccine provider records (on a vaccination card, or less commonly, in the mother's antenatal card) the administrated vaccine, the batch-number, date, and clinic name.

Infants who were up to three days of age at screening, who could suckle or feed, and who were staying in the study area for at least six months after enrolment were included in the trial.

Trained field workers used a prospective surveillance system (that monitored registered women aged 15-49 years for pregnancies and deliveries) to ascertain all births in the study area between August 2010 and November 2011. They enrolled eligible infants of consenting mothers in the trial and weighed them using calibrated electronic (38%) or spring (62%) scales. They recorded birth weights to the nearest 0.1kg (electronic scales) or 0.2kg (spring scales). All but five infants (0.2%) were weighed within 72 hours of delivery. At enrolment, field workers collected data on infant, maternal and household characteristics. Data on vaccination status (written record and maternal recall) were collected at monthly follow-up visits.

Infants were categorised as a) vaccinated, known vaccination date (if they had a plausible vaccination date on their vaccination card); b) vaccinated, unknown vaccination date (if they had an unknown or implausible date on their card); and c) unvaccinated (if either i) their card was viewed and had no evidence of vaccination, or ii) their card was not viewed (possibly because they did not have a card) but their caretaker consistently reported that they had never been vaccinated). In addition, infants whose card was never viewed and whose mothers reported they were vaccinated, but did not report which vaccine they received, were categorised as vaccination status unknown, as were those infants never seen in follow-up, with no information on their vaccination status.

We categorised infants as either non-low birth weight (NLBW) (weighing ≥2.50kg) or low birth weight (LBW) (2.00-2.49kg, 1.50-1.99kg, and <1.50kg). Neonatal illness was a health facility admission in the neonatal period (0-27 days of age).

Infants with known vaccination status, in follow-up at the end of the neonatal period, and having complete covariate data were eligible for inclusion in the analyses.

Analytical methods

We conducted all analyses using STATA 14.1 (STATACORP, 2015). As neonatal BCG vaccination is a frequent event, we calculated adjusted odds ratios (AOR) for the less frequent outcome of non-vaccination (rather than for vaccination) using multivariable logistic regression. The resulting AORs for this less frequent outcome thus approximated more closely to risk or rate ratios. Model building was informed by a hierarchical framework[5] of the determinants of vaccination identified a priori.[3 4 13 14] We initially fit a model comprising distal determinants (religion, ethnicity, socioeconomic status, maternal occupation, maternal education, vaccine due in wet season, infant sex); then added intermediate determinants (maternal age/ family size, maternal illness in the year before delivery, distance to the nearest health facility, place of delivery, multiple birth), followed by birth weight, and finally infant illness, a possible mediator of the association between birth weight and vaccination. We used likelihood ratio tests and 95% confidence intervals (95%CI) to assess statistical associations between each explanatory variable and vaccination.

We fitted interaction terms of birth weight and i) place of delivery, and ii) neonatal illness to the final model to assess whether either of these modified the association between birth weight and vaccination.

For all infants, irrespective of place of birth, we calculated BCG uptake rates at the end of the neonatal period and at 8, 12 and 52 weeks of age, stratified by birth weight, to examine variation by time since the due date. To assess how ensuring vaccination of facility-born infants prior to discharge would affect vaccination, we calculated 'theoretical' proportions vaccinated by assigning these infants as vaccinated in the neonatal period. We calculated the proportional increase in vaccination by dividing the theoretical proportion by the actual proportion for each time-period.

The ethics committees of the World Health Organisation (WHO), the London School of Hygiene & Tropical Medicine (LSHTM) and the KHRC granted approval for the Neovita trial. No additional ethics approval was needed for this study.

The Bill and Melinda Gates Foundation funded the Neovita trial.

RESULTS

Of 22955 infants enrolled in Neovita, 22217 (96.8%) were included in the analyses. Among 738 excluded, 362 were BCG vaccination status unknown, 242 were BCG vaccinated with an unknown date, 88 were lost-to-follow up in the neonatal period, and 46 were missing covariate data. Of those excluded, 275 died in the neonatal period. Table 1 shows that excluded infants were more likely to have LBW, to live further from a health facility, to be a multiple birth and to have poorer mothers.

Table 1: Baseline characteristics of infants included in the analyses of determinants of neonatal BCG vaccination.

Variable	Excluded Total=738	Included Total = 22217
Distal Determinants		
Religion of head of household		
Christian	471 (63.8)	15508 (69.8)
Muslim	201 (27.2)	5310 (23.9)
None/Traditional/Other	66 (8.9)	1399 (6.3)
Ethnicity		
Akan	317 (43.0)	10376 (46.7)
Non-Akan	421 (57.0)	11841 (53.3)
Socioeconomic status		
1 (poorest)	185 (25.1)	4325 (19.5)
2	174 (23.6)	4376 (19.7)
3	150 (20.3)	4433 (20.0)
4	125 (16.9)	4519 (20.3)
5(richest)	103 (14.0)	4564 (20.5)
Missing Values	1 (0. 1)	
Maternal occupation		
Gov/Private/ Other	31 (4.2)	1194 (5.4)
Self-employed	232 (31.4)	8714 (39.2)
Farming	251 (34.0)	6420 (28.9)
Does not work	224 (30.4)	5889 (26.5)
Maternal education		
None	264 (35.8)	6863 (30.9)
Primary school	138 (18.7)	4098 (18.5)
Secondary / tertiary	322 (43.6)	11256 (50.7)
Missing Values	14 (1.9)	
Vaccine due in wet season	461 (62.5)	14494 (65.2)
Sex, Female	340 (46.1)	10966 (49.4)
Intermediate Determinants		
Maternal age / Family size		
<20 years	114 (15.4)	2531 (11.3)
20-29; 1-3 children	263 (35.6)	7815 (35.2)
20-29; ≥4 children	120 (16.3)	3843 (17.3)
≥30; 1-3 children	29 (3.9)	1108 (5.0)
≥30; ≥4 children	182 (24.7)	6920 (31.2)
Missing Values	30 (4.1)	
Maternal illness in year before delivery	32 (4.3)	1091 (4.9)
Distance		
<1.00km	409 (55.5)	13471 (60.6)
1.00-4.99km	152 (20.6)	5133 (23.1)
>=5.00km	174 (23.6)	3613 (16.3)
Missing Values	2 (0.3)	
Facility delivery	517 (70.1)	17064 (76.8)
Multiple birth	52 (7.1)	795 (3.6)
Proximal Variables		
Birth weight		
>=2.5kg	520 (70.5)	18841 (84.8)
2.00-2.49kg	121 (16.4)	2910 (13.1)
1.50-1.99kg	59 (8.0)	385 (1.7)
<1.50kg	36 (4.8)	81 (0.4)
Missing Values	2 (0.3)	

Mediating Variables		
Neonatal illness	31 (4.2)	426 (1.9)

Infants were BCG vaccinated at a median of 8 days; 77% were vaccinated by the end of the neonatal period. Uptake decreased with declining birth weight, and was lowest (60%) among infants weighing <1.50kg. There was a strong dose-response relationship between LBW and the odds of non-vaccination in the neonatal period (p-trend<0.0001), after adjustment for other variables (Table 2). Infants weighing 1.50-1.99kg (AOR=1.64; 95%CI:1.30-2.08) and those weighing <1.50kg (AOR=2.42; 95%CI:1.50-3.88) had odds of non-vaccination 1.6 times and 2.4 times those of NLBW infants.

Table 2: Determinants of non-vaccination with BCG in the neonatal period

	Not Vaccinated / Total	Proportion not vaccinated (95%CI)	Unadjusted Odds Ratios	Adjusted for distal determinants	Adjusted for distal & intermediate determinants	Adjusted for distal, intermediate & proximal determinants (final model)	Final model adjusted for mediating effects of infant illness	Final model; among infants born in a health facility
			OR (95%CI) (p-value)	**AOR (95%CI) (p-value)**	**AOR (95%CI) (p-value)**	**AOR (95%CI) (p-value)**	**AOR (95%CI) (p-value)**	**AOR (95%CI) (p-value)**
Distal Variables								
Religion of head of household								
Christian	3387/15508	21.8 (21.2-22.5)	Ref	Ref	Ref	Ref	Ref	Ref
Muslim	1310/5310	24.7 (23.5-25.8)	1.17 (1.09-1.26)	1.04 (0.95-1.13)	1.01 (0.93-1.10)	1.01 (0.93-1.11)	1.01 (0.93-1.11)	1.00 (0.89-1.11)
None/Traditional/Other	392/1399	28.0 (25.7-30.4)	1.39 (1.23-1.58)	0.96 (0.85-1.09)	0.90 (0.79-1.03)	0.90 (0.79-1.03)	0.90 (0.79-1.03)	0.86 (0.72-1.03)
			(<0.0001)	(0.5416)	(0.2438)	(0.2445)	(0.2439)	(0.2440)
Ethnicity								
Akan	1891/10376	18.2 (17.5-19.0)	Ref	Ref	Ref	Ref	Ref	Ref
Non-Akan	3198/11841	27.0 (26.2-27.8)	0.60 (0.56-0.64)	0.91 (0.84-0.99)	0.94 (0.86-1.02)	0.93 (0.86-1.02)	0.93 (0.86-1.02)	0.96 (0.87-1.06)
			(<0.0001)	(0.0320)	(0.1381)	(0.1112)	(0.1099)	(0.4092)
Socioeconomic status								
1 (poorest)	1618/4325	37.4 (36.0-38.9)	5.19 (4.63-5.82)	3.90 (3.42-4.44)	2.70 (2.35-3.10)	2.69 (2.34-3.08)	2.68 (2.33-3.08)	2.98 (2.53-3.50)
2	1271/4376	29.0 (27.7-30.4)	3.56 (3.17-3.99)	2.91 (2.57-3.29)	2.33 (2.05-2.65)	2.32 (2.04-2.64)	2.32 (2.04-2.64)	2.34 (2.03-2.71)
3	1020/4433	23.0 (21.8-24.3)	2.60 (2.31-2.92)	2.27 (2.01-2.57)	1.98 (1.75-2.24)	1.98 (1.74-2.24)	1.98 (1.74-2.24)	1.98 (1.72-2.26)
4	709/4519	15.7 (14.7-16.8)	1.62 (1.43-1.83)	1.50 (1.32-1.70)	1.42 (1.25-1.61)	1.41 (1.24-1.60)	1.41 (1.24-1.60)	1.47 (1.28-1.68)
5 (richest)	471/4564	10.3 (9.5-11.2)	Ref	Ref	Ref	Ref	Ref	Ref
			(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)*	(<0.0001)
Maternal occupation								
Gov/Private/Other	158/1194	13.2 (11.4-15.3)	0.73 (0.61-0.87)	0.89 (0.75-1.07)	0.92 (0.76-1.10)	0.91 (0.76-1.09)	0.91 (0.76-1.10)	0.92 (0.75-1.12)
Self-employed	1500/8714	17.2 (16.4-18.0)	Ref	Ref	Ref	Ref	Ref	Ref
Farming	2082/6420	32.4 (31.3-33.6)	2.31 (2.14-2.49)	1.33 (1.22-1.46)	1.21 (1.11-1.33)	1.21 (1.11-1.33)	1.21 (1.11-1.33)	1.24 (1.11-1.39)
Does not work	1349/5889	22.9 (21.9-24.0)	1.43 (1.32-1.55)	1.19 (1.09-1.30)	1.13 (1.03-1.24)	1.13 (1.03-1.24)	1.13 (1.03-1.24)	1.18 (1.06-1.32)
			(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
Maternal education								
None	2032/6863	29.6 (28.5-30.7)	1.95 (1.81-2.09)	1.13 (1.03-1.24)	1.15 (1.05-1.26)	1.15 (1.05-1.27)	1.15 (1.05-1.27)	1.13 (1.01-1.27)
Primary school	1057/4098	25.8 (24.5-27.2)	1.61 (1.48-1.75)	1.18 (1.08-1.29)	1.17 (1.07-1.28)	1.17 (1.06-1.28)	1.17 (1.06-1.28)	1.17 (1.05-1.31)
Secondary / tertiary	2000/11256	17.8 (17.1-18.5)	Ref	Ref	Ref	Ref	Ref	Ref
			(<0.0001)	(0.0013)	(0.0013)	(0.0015)	(0.0015)	0.0138
Vaccine due in wet season								
Yes	3272/14494	22.6 (21.9-23.3)	Ref	Ref	Ref	Ref	Ref	Ref
No	1817/7723	23.5 (22.6-24.5)	1.06 (0.99-1.13)	1.04 (0.97-1.11)	1.04 (0.97-1.12)	1.04 (0.97-1.12)	1.04 (0.97-1.12)	1.05 (0.97-1.15)
			(0.1082)	(0.2274)	(0.2284)	(0.2353)	(0.2402)	0.2121

Sex								
Male	2701/11251	24.0 (23.2-24.8)	Ref	Ref	Ref	Ref	Ref	Ref
Female	2388/10966	21.8 (21.0-22.6)	0.88 (0.83-0.94)	0.87 (0.82-0,93)	0.86 (0.80-0.92)	0.85 (0.80-0.91)	0.85 (0.80-0.91)	0.83 (0.77-0.90)
			(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Intermediate Variables								
Maternal age / Family size								
<20 years	650/2531	25.7 (24.0-27.4)	1.10 (98.8-1.22)		1.22 (1.07-1.39)	1.19 (1.04-1.35)	1.19 (1.04-1.35)	1.27 (1.09-1.48)
20-29; 1-3 children	1601/7815	20.5 (19.6-21.4)	0.82 (0.76-0.88)		1.10 (1.01-1.20)	1.09 (1.00-1.19)	1.09 (1.00-1.19)	1.09 (0.98-1.22)
20-29; ≥4 children	1008/3843	26.2 (24.9-27.6)	1.13 (1.03-1.24)		1.11 (1.01-1.22)	1.11 (1.10-1.22)	1.11 (1.01-1.22)	1.14 (1.01-1.29)
≥30; 1-3 children	173/1108	15.6 (13.6-17.9)	0.59 (0.50-0.70)		0.93 (0.77-1.11)	0.92 (0.76-1.10)	0.92 (0.76-1.10)	0.97 (0.78-1.19)
≥30; ≥4 children	1657/6920	23.9 (23.0-25.0)	Ref		Ref	Ref	Ref	Ref
			(<0.0001)		(0.0080)	(0.0186)	(0.0191)	(0.0194)
Maternal illness in year								
before delivery	4840/21126	22.9 (22.3-23.5)	Ref		Ref	Ref	Ref	Ref
No	249/1091	22.8 (20.4-25.4)	1.00 (0.86-1.15)		0.94 (0.80-1.09)	0.93 (0.80-1.08)	0.93 (0.80-1.08)	0.92 (0.76-1.11)
Yes			(0.9468)		(0.3866)	(0.3568)	(0.3545)	(0.3764)
Distance from health facility								
<1.00km	2570/13471	19.1 (18.4-19.8)	Ref		Ref	Ref	Ref	Ref
1.00-4.99km	1146/5133	22.3 (21.2-23.5)	1.22 (1.13-1.32)		1.06 (0.98-1.16)	1.06 (0.98-1.15)	1.06 (0.98-1.15)	1.06 (0.96-1.17)
>=5.00km	1373/3613	38.0 (36.4-39.6)	2.60 (2.40-2.82)		1.37 (1.25-1.50)	1.37 (1.25-1.49)	1.37 (1.25-1.49)	1.60 (1.41-1.81)
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Place of birth								
Facility	3079/17064	18.0 (17.5-18.6)	Ref		Ref	Ref	Ref	
Non-facility	2010/5153	39.0 (37.7-40.3)	2.90 (2.71-3.11)		1.83 (1.69-1.98)	1.82 (1.69-1.98)	1.83 (1.69-1.98)	
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	
Multiple birth								
No	4898/21422	22.9 (22.3-23.4)	Ref		Ref	Ref	Ref	Ref
Yes	191/795	24.0 (21.2-27.1)	1.07 (0.90-1.26)		1.08 (0.91-1.29)	0.93 (0.78-1.13)	0.93 (0.78-1.13)	1.00 (0.81-1.23)
			(0.4468)		(0.3692)	(0.4742)	(0.4747)	(0.9889)
Proximal Variables								
Birth weight								
>=2.5kg	4204/18841	22.3 (21.7-22.9)	Ref			Ref	Ref	Ref
2.00-2.49kg	737/2910	25.3 (23.8-26.9)	1.18 (1.08-1.29)			1.08 (0.98-1.19)	1.08 (0.98-1.19)	1.12 (0.99-1.27)
1.50-1.99kg	116/385	30.1 (25.7-34.9)	1.50 (1.20-1.87)			1.64 (1.30-2.08)	1.64 (1.30-2.08)	1.69 (1.28-2.22)
<1.50kg	32/81	39.5 (29.4-50.6)	2.27 (1.45-3.55)			2.41 (1.50-3.88)	2.42 (1.51-3.89)	2.29 (1.35-3.90
			(<0.0001)			(<0.0001)	(<0.0001)*	(0.0001)
Mediating Variable								
Neonatal illness								
No	5009/21791	23.0 (22.4-23.5)	Ref				Ref	Ref
Yes	80/426	18.8 (15.3-22.8)	0.77 (0.61-0.99)				0.91 (0.71-1.17)	0.89 (0.66-1.20)
			(0.0363)				(0.4627)	(0.4542)

** p-trend = <0.0001*

Not being born in a health facility (compared to being born in a health facility), living 5km or more from the nearest health facility (compared to living within 1km of a health facility), and being in the lowest quintile of socioeconomic status (SES) (compared to the highest) were all strongly associated with not receiving BCG in the neonatal period (Table 2). Almost 40% of home-born infants were BCG unvaccinated, and their odds of non-vaccination were 1.82 times those of facility-born infants (AOR=1.82; 95%CI:1.69-1.98; p=<0.0001). Infants living >5km from a health facility had odds of non-vaccination 1.37 those of infants living within 1km (AOR=1.37; 95%CI:1.25-1.49; p=<0.0001), even after adjusting for place of birth and other factors. A strong dose response relationship was observed between SES and neonatal BCG vaccination (p-trend <0.0001), with infants from the poorest quintile of SES having odds of non-vaccination 2.7 times greater than those from the wealthiest quintile (AOR=2.69; 95%CI:2.34-3.08) even after adjustment for all other explanatory variables.

Being a farmer or unemployed (compared to being self-employed), having primary school education or no education (compared to secondary/tertiary education) and being aged less than 20 years of age (compared to being aged 30 or more with four or more children) were associated with an increased odds of non-vaccination in the final model. Conversely, female infants had lower odds of non-vaccination(Table 2).

There was little variation in the effect size for the distal factors, after adjustment for intermediate and proximal mediating variables, and in the effect size for intermediate level factors after adjustment for birth weight. Illness did not appear to mediate the effect of birth weight or any other determinants of vaccination (Table 2).

There was little evidence that either place of delivery or infant illness modified the association between birth weight and vaccination (p-value for interaction all >0.2).

Additional analyses of the vaccination of facility-born infants

As a post-hoc analysis we further explored the vaccination of facility-born infants. We analysed their age at vaccination, and analysed their determinants of vaccination.

Facility-born infants were vaccinated at a median age of 6 days (IQR=17). The effect estimates for the determinants of vaccination were very similar to those for the entire study population. The most important effect was for infants living >5km from a health facility, (AOR=1.60; 95%CI:1.41-1.81) (Table 2).

Impact of vaccinating all facility-born infants before discharge

Overall BCG uptake was 77.1% (95%CI:76.5-77.6) by the end of the neonatal period, 91.8% (95%CI:91.4-92.1) by 8 weeks of age; 95.9% (95%CI:95.6-96.1) by 12 weeks of age, and 98.7% (95%CI:98.5-98.8) by 52 weeks of age (Table 3). At each of these time points, uptake declined with decreasing birth weight, although there was little difference at age 52 weeks (Table 3). We calculated that 91.0% (95%CI:90.6-91.3) of all infants, 91.2% (95%CI:87.9-93.6) of infants weighing 1.50-1.99kg, and 88.9% (95%CI:79.9-94.1) of infants weighing <1.50kg may have been vaccinated in the neonatal period if all facility-born infants were vaccinated prior to discharge. This represented a respective 18%, 31% and 47% increase in vaccine uptake by the end of the neonatal period. Similar smaller gains in vaccine uptake would have occurred for the other categories of birth weight (Table 3).

Table 3: BCG uptake rates at 4, 8, 12 and 52 weeks of age by birth weight, and rates that could be achieved if all those born in a facility had been vaccinated prior to discharge from the facility.

	BCG Uptake Rates		
Birth weight	**Actual**	**Theoretical**	**% Increase in Vaccine Uptake**
		Age 4 weeks	
>=2.5kg	77.7 (77.1-78.3)	91.2 (90.8-91.6)	17.4
2.00-2.49kg	74.7 (73.1-76.2)	89.4 (88.2-90.5)	19.7
1.50-1.99kg	69.9 (65.1-74.3)	91.2 (87.9-93.6)	30.5
<1.50kg	60.5 (49.4-70.6)	88.9 (79.9-94.1)	46.9
Overall	77.1 (76.5-77.6)	91.0 (90.6-91.3)	18.0
		Age 8 weeks	
>=2.5kg	92.1 (91.7-92.5)	96.7 (96.4-96.9)	5.0
2.00-2.49kg	90.4 (89.3-91.4)	95.7 (94.9-96.4)	5.9
1.50-1.99kg	87.5 (83.8-90.5)	97.9 (95.9-99.0)	11.9
<1.50kg	72.8 (62.1-81.4)	91.4 (82.9-95.8)	25.5
Overall	91.8 (91.4-92.1)	96.5 (96.3-96.8)	5.1
		Age 12 weeks	
>=2.5kg	96.1 (95.8-96.4)	98.2 (98.1-98.4)	2.2
2.00-2.49kg	95.1 (94.2-95.8)	97.8 (97.2-98.2)	2.8
1.50-1.99kg	93.8 (90.9-95.8)	98.4 (96.6-99.3)	4.9
<1.50kg	88.9 (79.9-94.1)	97.5 (90.6-99.4)	9.7
Overall	95.9 (95.6-96.1)	98.2 (98.0-98.4)	2.4
		Age 52 weeks	
>=2.5kg	98.8 (98.6-98.9)	99.5 (99.4-99.6)	0.1
2.00-2.49kg	98.1 (97.5-98.5)	99.1 (98.7-99.4)	1.0
1.50-1.99kg	97.4 (95.2-98.6)	99.5 (97.9-99.9)	2.2
<1.50kg	96.3 (89.1-98.8)	98.8 (91.7-99.8)	2.6
Overall	98.7 (98.5-98.8)	99.4 (99.3-99.5)	0.7

DISCUSSION

Our analyses indicate that LBW infants are at high risk of missing BCG vaccination in the neonatal period. There appears to be a dose-response relationship between vaccination and birth weight; vaccination declines with decreasing birth weight, regardless of place of birth.

We excluded sicker weaker infants who were unable to feed at enrolment, as well as those who died during the neonatal period. The LBW infants included in our analyses were probably well, and illness was probably not a contraindication to vaccination. Our finding that neonatal illness did not appear to mediate the association between birth weight and vaccination, overall or when stratified by place of delivery, supports this. LBW is not a contraindication to vaccination, and LBW infants are recommended to be vaccinated at the same chronological age as NLBW infants;[15] however, our results indicate that this recommendation is not being optimally adhered to in Ghana.

We identified a number of additional determinants of neonatal BCG vaccination, including place of delivery, distance to health facility, SES, and maternal education, occupation and age. These were also identified as determinants in our analyses of postneonatal vaccination,[5] and other analyses,[16] and reflect broader inequities in access to care in our study population.

In our study area, > 20% of the 77% of facility-born infants were unvaccinated at the end of the neonatal period, demonstrating a lack of compliance with the routine schedule. This was double for infants weighing <1.5kg at birth.

Vaccination was even lower among home-born infants, suggesting parental delay in accessing vaccination services, or for those living far from a facility, the monthly scheduling of mobile outreach clinics. The fact that home-born LBW infants are even more delayed may reflect parental reluctance to bring fragile infants for vaccination, as previously documented in a review of unpublished surveys.[6]

Facility-born infants were vaccinated at a median age of six days, suggesting that many are unvaccinated at discharge following delivery; they may instead be referred to the child health clinic for vaccination. This would explain why birth weight and other maternal and household factors remain as vaccine determinants among facility-born infants. If true, then this practice is allowing inequities in vaccination to persist. A single vial of BCG vaccinates twenty infants. Fear of wastage has previously been cited as a reason for missing opportunities for vaccination,[17] and may be a motivation for referring facility-born infants to the child health clinic for vaccination.

Overall uptake of BCG vaccination at age 52 weeks was high; however, many infants were vaccinated late, including a higher proportion of LBW infants. BCG vaccination is known to have an important protective effect against TB meningitis in the first five years of life[18]. Timely vaccination is important so as not to prolong the risk of infection. Furthermore, timeliness of vaccination is increasingly recognised as an important indicator of the overall quality of vaccination programmes[19], and our finding that LBW infants were less likely to be in compliance with the routine schedule, highlights them as a group who are underserved by vaccination. The Global Vaccine Action Plan[2] advocates for identifying groups who are underserved by routine vaccination services so that they can be targeted for vaccination, and so that inequities in the delivery of the vaccination programme can be reduced. Ensuring vaccination of facility-born infants prior to discharge would optimise compliance with the recommended schedule and the timeliness of BCG vaccination.

Our finding of reduced vaccination of LBW infants is consistent with our previous finding of delayed postneonatal vaccination (with DTP1 and DTP3) of LBW infants.[5]. It also supports recent findings[20] from Nairobi Kenya, that infants weighing <2.00kg living in informal urban settlements took 9 times longer to be vaccinated in the first 90 days of life than NLBW infants. The difference in the magnitude of the association between our study and the Kenyan study may be due to the exclusion of unvaccinated infants, the lower prevalence of LBW (6%), the higher proportion of facility-born infants (96%), and the higher proportion of private facility-born infants (67%) in the Kenyan study.

Data from Guinea Bissau[21] also suggested lower BCG vaccination among LBW infants. As there was reportedly a national policy of delaying vaccination of LBW infants until they had gained weight or attended for DTP vaccination, these results are not generalisable to countries, such as Ghana, where no such policy exists.

A study from Nigeria[22] reported delayed vaccination of under-nourished children. This study provides indirect evidence of the effect of birth weight, in addition to infant feeding and illness (the causes of undernourishment[23]) on BCG vaccination.

Strengths

Our study was strengthened by low loss to follow-up rates (<3%), by the population-based nature of the sample and by the collection of high quality data on both birth weight and vaccination.

Limitations

We lacked qualitative data on the practices associated with vaccination following delivery, including the reasons why infants born in health facilities were not getting vaccinated, and why LBW infants born in health facilities were less likely to be vaccinated. This limits our understanding of the barriers to neonatal vaccination (among both facility-born and home-born infants), and to the vaccination of LBW infants.
A large number of variables were included in our models, thus increasing the possibility of type-1 errors. Due to small numbers, our study was underpowered to detect differences in analyses where birth weight was stratified by factors such as infant illness. Although we demonstrated that vaccinating all facility-born infants prior to discharge could substantively improve the timing and equity of delivery of BCG vaccination, this finding may not be generalizable to settings where most infants are born at home.

CONCLUSIONS

Our analyses indicate that LBW is a risk factor for not being vaccinated with BCG in the neonatal period, even for facility-born LBW infants. Efforts to improve neonatal vaccination, especially for LBW infants, are warranted, regardless of where they are born. For LBW infants born in facilities, vaccination prior to discharge is recommended.

Qualitative studies to understand the reasons for non-vaccination with BCG in the neonatal period are needed. In particular studies are needed to understand why infants, including LBW infants born in health facilities are not getting vaccinated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Delayed BCG vaccination was associated with low birth weight (LBW) among primarily facility born infants in urban slums in Kenya.

Undernourishment (caused by LBW, illness and feeding practices) was also associated with delayed BCG vaccination in urban Nigeria.

WHAT THIS STUDY ADDS

This large, generalisable prospective population-based cohort study in rural Ghana demonstrates lower compliance with the BCG vaccination schedule among LBW compared to non-LBW infants.

LBW is a strong determinant of neonatal BCG vaccination, with a dose response relationship between birth weight and vaccination.

The association persists even for facility-born LBW infants, suggesting a lack of compliance with policy to vaccinate prior to discharge from the facility.

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CONTRIBUTIONS

MOL drafted the report, and it was reviewed by all authors. MOL, ST, SF, and KE designed the study and analyses. KE, BK, and SN designed the trial. CS, MOL, GT, SN, LH, and KE were responsible for trial conduct. GT coordinated the fieldwork. MOL and CS managed the database. MOL undertook the statistical analyses with input from ST and SF.

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